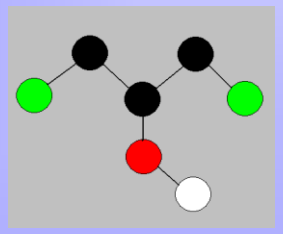
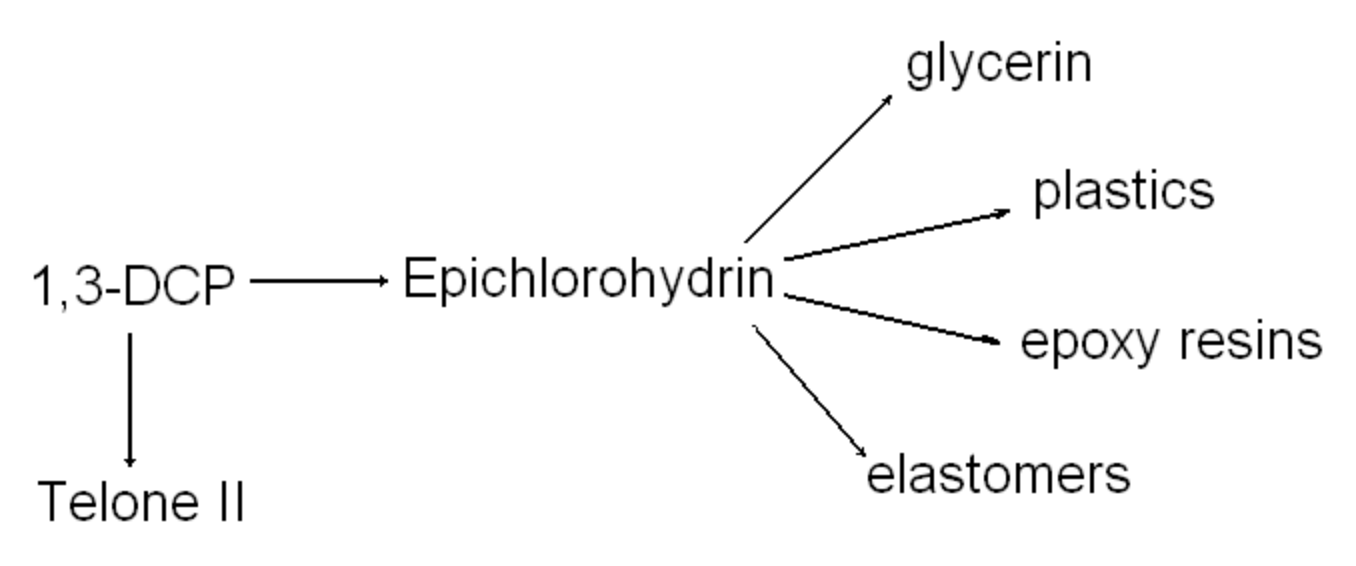
HAZARD IDENTIFICATION EVIDENCE FOR 1,3-DICHLORO-2-PROPANOL (1,3-DCP)

Cancer Toxicology and Epidemiology Section
Reproductive and Cancer Hazard Assessment Branch



USE OF 1,3-DCP

1,3-DCP is a high production volume industrial chemical.



1,3-DCP in FOODS

- Formed in some foods during processing
- Present in foods to which acid-hydrolyzed vegetable protein has been added
- From packaging
- Water treatment contaminant

OVERVIEW OF CARCINOGENICITY EVIDENCE

- **Animal Carcinogenicity Data (Hercules, 1989)**
- **Genotoxicity**
- ***In Vitro* Cell Transformation Assay**
- **Metabolism**
- **Structure Activity Considerations**
- **Possible Mechanisms**

ANIMAL STUDIES

- **Carcinogenicity assays in male and female Wistar Han KFM rats, 104-weeks, drinking water**
- **Chronic toxicity assays in male and female Wistar Han KFM rats 26-, 52- and 78-weeks, drinking water**

104-WEEK CARCINOGENICITY DRINKING WATER ASSAYS

- **Wistar Han KFM rats (50 each sex, dose)**
  - Male rats: 0, 2.1, 6.3, 19 mg/kg/day
  - Female rats: 0, 3.4, 9.6, 30 mg/kg/day
- **Complete histopathology**
  - All control & high-dose animals
  - Low- & mid-dose animals dying before week 104
- **Limited histopathology (adrenal, esophagus, kidney, lungs, thyroid, tongue)**
  - Low- & mid-dose animals surviving to week 104

TUMOR INCIDENCES IN MALE RATS (1)

Tumor Site/Type	Dose (mg/kg bw/day)			
	0	2.1	6.3	19
KIDNEY				
Tubular adenomas	0/50 p<.001	0/50	3/50	9/50 p<.05
Tubular carcinomas	0/50	0/50	0/50	1/50
Adenomas and carcinomas	0/50 p<.001	0/50	3/50	9/50 p<.05
LIVER				
Hepatocellular adenomas	1/50	0/50	0/50	0/50
Hepatocellular carcinomas	0/50 p<.001	0/50	2/50	8/50 p<.05
Adenomas and carcinomas	1/50 p<.001	0/50	2/50	8/50 p<.05
Hemangiosarcoma	0/50	0/50	0/50	1/50

TUMOR INCIDENCES IN MALE RATS (2)

Tumor Site/Type	Dose (mg/kg bw/day)			
	0	2.1	6.3	19
THYROID				
Follicular adenomas	0/50 p<.05	0/50	2/50	3/48
Follicular carcinomas	0/50	0/50	2/50	1/48
Adenomas and carcinomas	0/50 p<.05	0/50	4/50	4/48 p=.052
TONGUE				
Squamous cell papillomas	0/50 p<.001	1/50	0/49	6/50 p<.05
Squamous cell carcinomas	0/50 p<.001	0/50	0/49	6/50 p<.05
Papillomas and carcinomas	0/50 p<.001	1/50	0/49	12/50 p<.001
OTHER ORAL CAVITY (NON-TONGUE)				
Papillary carcinomas	0/50	0/50	0/50	2/50

TUMOR INCIDENCES IN FEMALE RATS (1)

Tumor Site/Type	Dose (mg/kg bw/day)			
	0	3.4	9.6	30
LIVER				
Hepatocellular adenomas	1/50 p<.05	1/50	1/50	5/50
Hepatocellular carcinomas	0/50 p<.001	0/50	1/50	36/50 p<.001
Adenomas & carcinomas	1/50 p<.001	1/50	2/50	41/50* p<.001
Hemangio-sarcoma	0/50	0/50	0/50	1/50

*25% metastasized to lungs

TUMOR INCIDENCES IN FEMALE RATS (2)

Tumor site/type	Dose (mg/kg bw/day)			
	0	3.4	9.6	30
THYROID (follicular cells)				
Adenomas	1/50	0/50	3/50	3/49
Carcinomas	0/50	0/50	0/50	2/49
Adenomas & carcinomas	1/50 P<.05	0/50	3/50	5/49
TONGUE (squamous cells)				
Papillomas	0/50 P<.001	0/50	0/50	7/49 P<.01
Carcinomas	0/50 P<.001	1/50	1/50	4/49 P=.056
Papillomas & carcinomas	0/50 P<.001	1/50	1/50	11/49 P<.001
OTHER ORAL CAVITY (non-tongue)				
Papillary carcinomas	0/50	0/50	1/50	0/50

78-WEEK CHRONIC TOXICITY STUDY – MALE RATS

Tumor Site/Type	Dose (mg/kg bw/day)			
	0	2.1	6.3	19
KIDNEY				
Renal tubular adenoma	0/10	0/10	0/10	1/10
LIVER				
Hepatocellular carcinoma	0/10 p<.05	0/10	0/10	3/10
THYROID				
Thyroid follicular adenoma	0/10	0/10	1/10	0/10
TONGUE				
Squamous cell carcinoma	0/10	0/10	1/10	0/10

78-WEEK CHRONIC TOXICITY STUDY – FEMALE RATS

Tumor Site/Type	Dose (mg/kg bw/day)			
	0	3.4	9.6	30
LIVER				
Hepatocellular carcinoma	0/10 p<.001	0/10	0/10	7/10 p<.01
TONGUE				
Squamous cell papilloma	0/10	0/10	0/10	1/10

IN VITRO GENOTOXICITY DATA

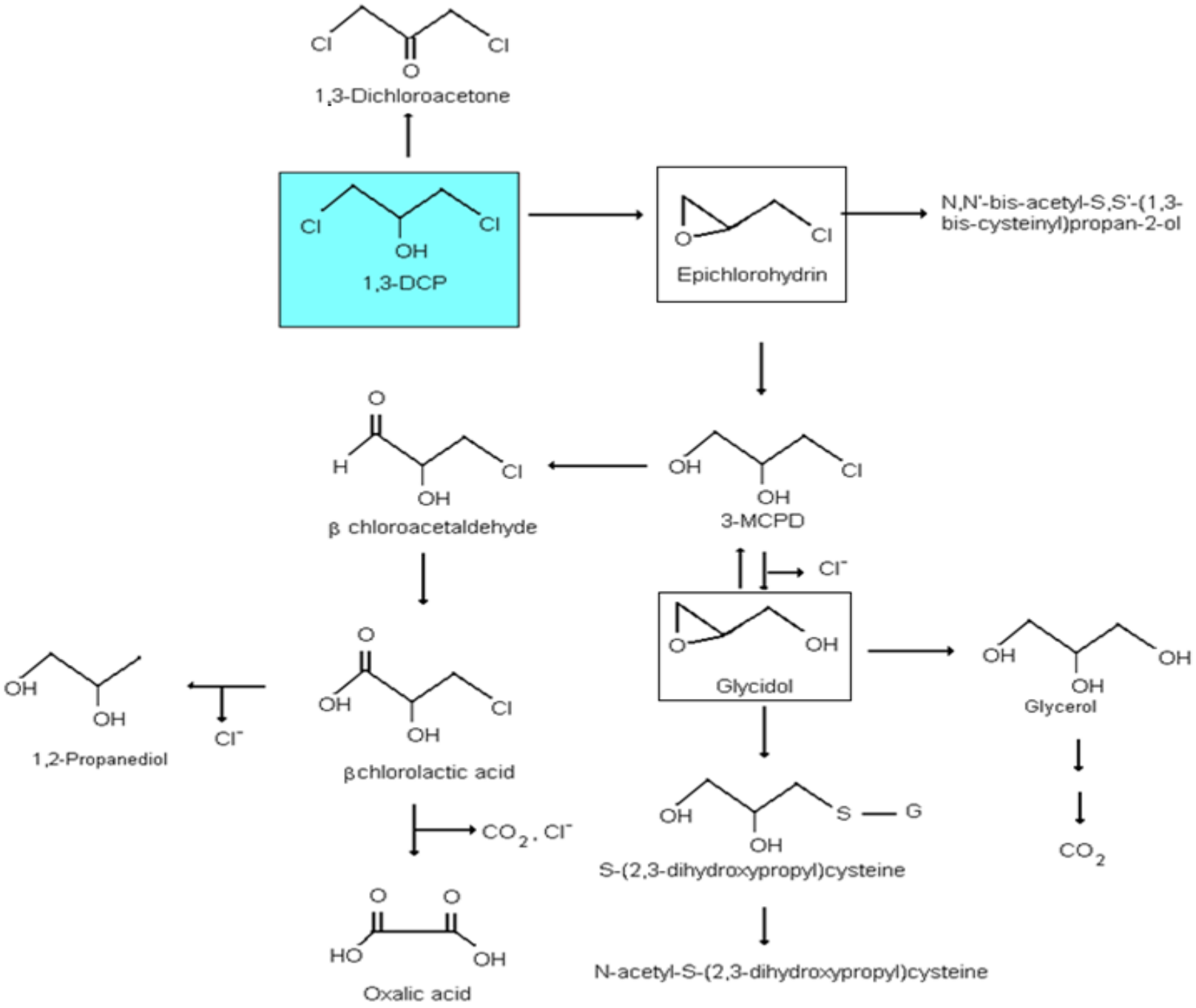
- **Positive in numerous *in vitro* assays in**
  - *Salmonella* reverse mutation assays
    - TA 97 and 98 (+S9) frameshift mutations
    - TA 100 and 1535 (+/- S9) base pair mutations
  - *Salmonella* forward mutation assays (+/- S9)
  - *E. coli* reverse mutation (+ S9)
  - *E. coli* DNA repair (+ S9)
  - Mammalian cell (mouse and human) mutation (+/- S9)
  - SCE in hamster (V79 and CHO) cells (+/- S9)
  - Chromosome aberrations in CHO cells (+/- S9)

IN VIVO GENOTOXICITY DATA

- **Negative in three *in vivo* assays in**
  - *Drosophila* somatic mutation (wing spot)
  - Wistar rat bone marrow micronucleus
  - Wistar rat unscheduled DNA synthesis (UDS)

MOUSE CELL *IN VITRO* MALIGNANT TRANSFORMATION ASSAY

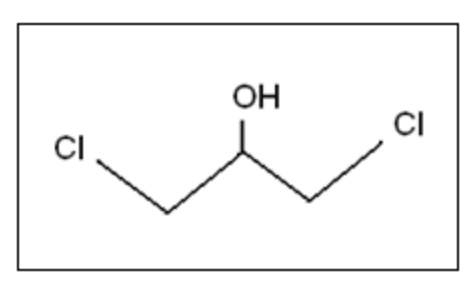
	1,3-DCP concentration (µg/mL)			
Number of transformed foci/number of treated dishes	Control	100	250	500
	0/24	7/14 p<.001	15/15 p<.001	3/14 p<.05


1,3-Dichloroacetone
1,3-DCP
Epichlorohydrin
N,N'-bis-acetyl-S,S'-(1,3-bis-cysteinyl)propan-2-ol
β chloroacetaldehyde
3-MCPD
Cl⁻
Glycidol
Glycerol
CO2
1,2-Propanediol
Cl⁻
βchlorolactic acid
CO2, Cl⁻
S-(2,3-dihydroxypropyl)cysteine
N-acetyl-S-(2,3-dihydroxypropyl)cysteine
Oxalic acid

STRUCTURE ACTIVITY CONSIDERATIONS

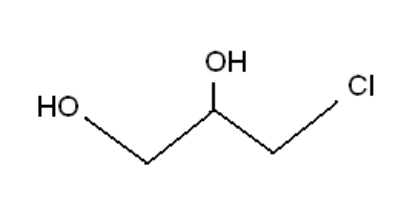
- 1,3-DCP and ten other structurally related halogenated compounds
- Seven of these are IARC and Proposition 65 carcinogens

Halogenated Propanols



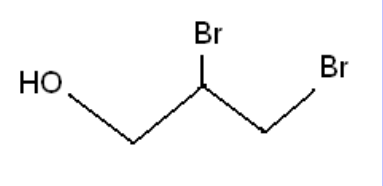
1,3-DCP

- Not evaluated by IARC



3-MCPD

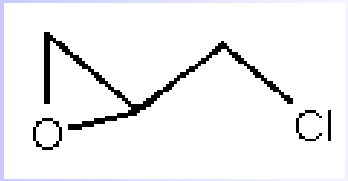
- Not evaluated by IARC



2,3-Dibromo-1-propanol

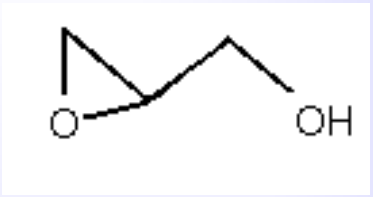
- IARC 2B
- Proposition 65

Three-carbon epoxides



Epichlorohydrin

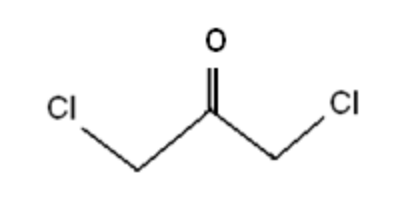
- IARC 2A
- Proposition 65



Glycidol

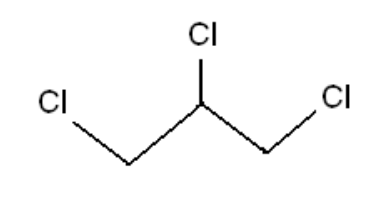
- IARC 2A
- Proposition 65

Other three-carbon halogenated compounds



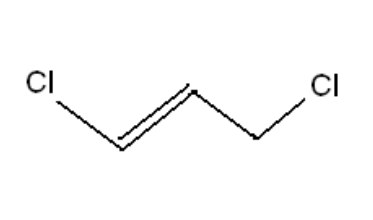
1,3-Dichloroacetone

- Not evaluated by IARC or Proposition 65



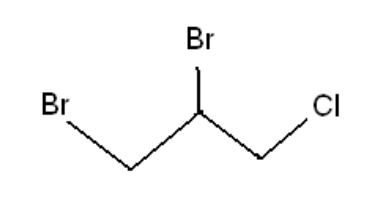
1,2,3-Trichloropropane

- IARC 2A
- Proposition 65



Telone II

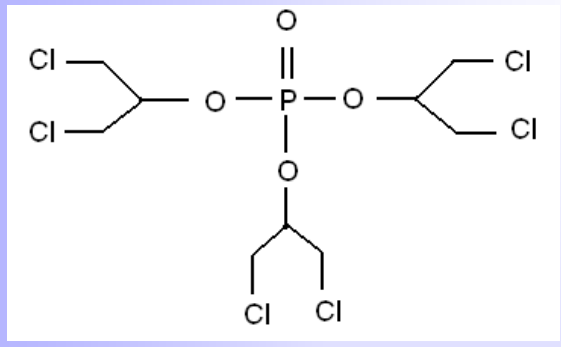
- IARC 2B
- Proposition 65



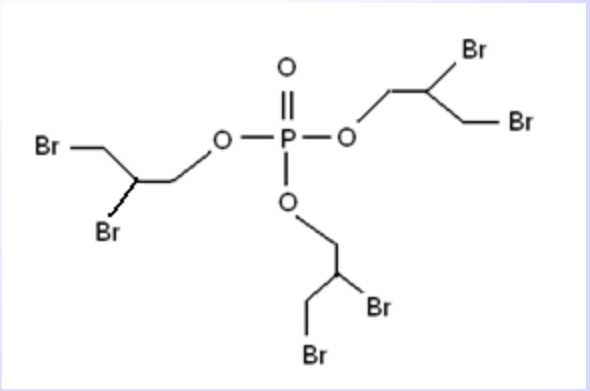
DBCP

- IARC 2B
- Proposition 65

Phosphate triesters



TDCPP



TDPP

- Not evaluated by IARC or Proposition 65

- IARC 2A
- Proposition 65

TUMOR SITE CONCORDANCE

Chemical	Liver		Kidney		Thyroid		Tongue or oral cavity	
	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
1,3-DCP		M F		M		M F		M F
3-MCPD				M F				
Glycidol	M				M	M		F
2,3-Dibromo-1-propanol	M	M F						F
1,2,3-Trichloro-propane	M F			M			F	M F
Telone II		M						
DBCP				M F				M F
TDCPP		M F		M F				
TDPP	F		M F	M F				M F

POSSIBLE MECHANISMS

- Genotoxicity
- Hepatotoxicity → hepatocarcinogenesis
- Direct contact carcinogenicity (tongue and oral cavity)

SUMMARY OF EVIDENCE

- **Animal evidence for carcinogenicity**
  - Tumors in both sexes of the rat (only species tested)
  - Tumors at multiple sites in males and females, including rare tongue tumors
  - Dose response
- **Genotoxicity in multiple *in vitro* assays with or without S9**
- ***In vitro* malignant transformation assay**
- **Metabolism to two epoxide carcinogens**
- **Structure activity considerations**
  - Structurally similar to seven carcinogens